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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/697,329 | 10/27/2000 | Eiichi Iishi | 1422-449P | 8402 |

7590 03/14/2003

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Falls Church, VA 22040-0747

EXAMINER

HABTE, KAHSAY

| ART UNIT | PAPER NUMBER |
|----------|--------------|
|----------|--------------|

1624

DATE MAILED: 03/14/2003

23

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/697,329

Applicant(s)

IISHI ET AL.

Examiner

Kahsay Habte, Ph. D.

Art Unit

1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 27 February 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 7 and 12-17 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 7 and 12-17 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 1/10/02 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 22.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

1. Claims 7 and 12-17 are pending.

Response to Amendment

2. Applicant's amendment filed 2/27/03 in response to the previous Office Action (Paper No. 20) is acknowledged. The prior art rejection of claim 7 has been maintained.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 7 and 12-15 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Kaspersen *et al.* {Journal of Label. comp. and Radiopharm., 27, No. 9, 1055 (1989)}. Kaspersen *et al.* teaches the multi-step synthesis of Org-3770 (mirtazapine) on page 1058 (Fig.4). On page 1066, Kaspersen *et al.* teaches the synthesis of mirtazapine and the crystallization of the mirtazapine (compound **1c**) from the crude product using methanol/water solvent mixture to achieve colorless crystals. Compound **1c** is ¹³carbon labeled product, but since the claim embraces the labeled compounds, the crystals product acquired from this process are identical to the claimed

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crystals of mirtazapine. The synthesis of compound **1d** on page 1067 also can be used as an additional prior art, even though Kaspersen et al. did not provide any information on the specific nature of the product (solid, crystal, or oily). Since compound **1c** and **1d** are the same compounds, therefore compound **1d** is also presumed to be crystal. These products (crystals from compound **1c**) including compound **1d**, are exactly the same compounds (crystals of mirtazapine) claimed by the applicants. In order to overcome this rejection, applicants have to replicate Kaspersen's and show that their product is different.

Response to arguments

Applicants arguments filed 02/27/2003 have been fully considered but they are not persuasive.

Applicants indicate that the ultimate object of their invention is to provide low hygroscopic crystals of mirtazapine that are useful as therapeutic agents, which are prepared by drying the crystals of a mirtazapine hydrate of inventive formula (I). Applicants admit that Mirtazapine compounds has been sold as pharmaceuticals useful as antidepressant in many countries including the United States. Applicants argue that Kaspersen's mirtazapine compound is used for the determination of the bioavailability and therefore, there is clearly no need to use the labeled compounds as pharmaceuticals for humans. They also indicate that the labeled compounds if administered to humans, could bring unwanted side effects. The examiner strongly disagrees with applicants. The use of labeled compounds is not only for monitoring the

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interaction of the pharmaceuticals in the body. Even the unlabeled compounds carry certain percent of the labeled isotopes in them. For example, carbon 13 has the natural abundance of 1%; that is, approximately 1% of all the carbon atoms in any sample of an organic compound are carbon-13 atoms. Thus, it is applicant's assumption that the labeled compounds are not used for the treatment of disorders. There is no indication that Kaspersen's mirtazapine are not suited for the treatment of depression. Applicants have to show evidence that the continuous administration of labeled compounds (Kaspersen's) to humans would bring unwanted side effects. Applicants are only speculating. As applicant's argument indicates, it seems that all labeled compounds are unfit for pharmaceutical purposes to treat certain diseases. As far as we know, the labeled and unlabeled crystal mirtazapine compounds can be administered to the body for treatment purposes. The use of labeled compound in research is in fact based on the assumption that they act the same as non-labeled.

Applicants also argue that Kaspersen do not disclose or suggest anhydrous mirtazapine that are prepared by pulverizing the mirtazapine hydrate. Kaspersen teach anhydrous crystals that are colorless and have a melting point of 123.8-125.8 °C (see page 1066). The examiner disagrees with applicants.

In regard to the limitation put into claims 12-15, a compound is a compound no matter what limitation is put into it.. According to MPEP 2112.01:

Where the claimed and prior art products are identical or substantially identical in

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structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). [underscoring added]

Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. In re Best, 562 F.2d at 1255, 195 USPQ at 433.

Applicants also failed to address the issues raised in previous Office Action, because they did not replicate Kaspersen's mirtazapine to prove that their compound is different from Kaspersen's. Applicants can overcome the rejection over the prior art by showing that their product is different from Kaspersen's.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 16 and 17 are rejected under 35 U.S.C. 102(b) as anticipated by Van der Burg et al (US Pat. No. 4,062,848). Claims 16 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by van der Burg et al (US Pat. No. 4,062,848). Van der Burg et al. teaches the pharmaceutical formulation of mirtazapine compounds on column 1 (line 7). Water solutions are one of the known formulations for pharmaceutical composition. Applicants claim pharmaceutical compositions of mirtazapine adduct that is the same as Van der Burg et al. Since a hydrate of mirtazapine in aqueous solution is a pharmaceutical composition and would be identical to a solution from the non-hydrate mirtazapine, the same material is obtained.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

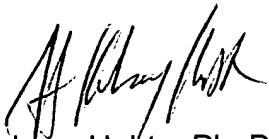
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Conclusion

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kahsay Habte, Ph. D. whose telephone number is (703) 308-4717. The examiner can normally be reached on M-F (9.00AM- 5:30PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mukund Shah can be reached on 703-308-4716. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.



Kahsay Habte, Ph. D.
Examiner
Art Unit 1624



Mark L. Berch
Primary Examiner
Art Unit 1624

KH
March 14, 2003